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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,534	06/18/2001	Bryan John Smith	1300-1-008	5753

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,534	SMITH, BRYAN JOHN	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/05 has been entered.

2. Applicant is reminded of Applicant's election of a hybrid protein having the antigen-binding antibody fragment linked to an albumin molecule or fragment thereof, the linkage being by a bridging molecule between the thiol groups of a cysteine residue that is present in the antibody and another such residue present in albumin at position 34, in the amendment filed 6/16/03.

Claims 14 and 16-22 read upon the elected species and are currently being examined.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 14 and 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado et al (British J. Cancer 73: 175-182, 1996) in view of US 5,714,142, WO 98/00171 A2, US 5,670,132 and Peters (IDS reference "AT").

Delgado et al teach that $F(ab')_2$ fragments of monoclonal antibody F9 is currently the most promising agent in clinical trials (especially last sentence of the first incomplete paragraph at column 2 on page 180). Delgado et al teach fab fragments are less effective than $F(ab')_2$ fragments (especially second column on page 180). Delgado et al teach that coupling PEG to antibody fragment $F(ab')_2$ to create a PEG-F9 conjugate increased the specificity of the antibody fragment for subcutaneous tumors due to increased plasma half-life as a consequence of reduced renal clearance and the resulting increased plasma and tissue levels (especially introduction). Delgado et al further teach that PEG-conjugation caused a reduction in antigen binding due to entry into and exit rates from tumor and normal tissues in a tissue specific fashion (especially abstract). Delgado et al teach use of the conjugate for both drug delivery and tumor imaging (especially first full paragraph at column 2 on page 180).

Delgado et al do not teach the hybrid protein/pharmaceutical composition thereof of the instant claims wherein an antigen binding antibody fragment is coupled to position 34 of albumin through a bridging agent of from around 10-20 angstroms in length, said agents including an optionally substituted hexylene, nor wherein the antibody fragment is a Fab or Fab' fragment optionally containing one or more additional amino acid residues, nor wherein the hybrid protein is covalently linked to one or more effector or reporter groups.

US 5,714,142 discloses that tremendous potential for exploiting highly potent and specific biological activities of peptides, proteins and other drugs has been limited by factors such as short half lives. US 5,714,142 discloses that albumin, a large stable protein that is too large to be filtered through the kidneys, has been conjugated to small molecule drugs, peptides or proteins to increase half-life when administered as a pharmaceutical composition. US 5,714,142 further discloses that Mao et al greatly increased the half-life of SOD, and that albumin coupling is an effective approach to increasing serum half-life (especially column 1 and column 2 through lines 1-3). US 5,714,142 discloses linker molecules such as optionally substituted alkylenes for example, hexylene (especially column 6, claims), and that the active agent that is coupled to a moiety that prevents renal excretion should be capable of derivitization without significant loss of activity (especially column 13 at lines 55-66), so the agent is caused to bind through a functional group or side chain that is not essential for pharmacological activity (especially column 15 at lines 1-6).

WO 98/00717 A2 teaches conjugates of drugs covalently coupled to blood components such as albumin, for example, via a linking polypeptide or alkylene of 6 carbon atoms through groups including thiol groups. WO 98/00717 A2 teaches that by coupling the drug to albumin, the activity of the drug is extended, i.e., the half-life is increased, that only one administration need be given during the active period of time, and greater specificity is achieved since the active compound or drug will be bound to a large molecule where it is less likely to be taken up intracellularly to interfere with other physiological processes. WO 98/00717 A2 exemplifies using hydroxyl groups to link drugs to albumin, said use resulting in multiple attachment sites and/or incomplete derivitization of at least half of the albumin molecules (see entire reference, especially abstract, page 5 at lines 23-29, page 6 at lines 1-8, page 8 at lines 12-17 and page 12 at lines 16-20).

US 5,670,132 discloses PEG-coupled –TC-99m-radiolabeled antibody fragments that are useful for radioimmunodetection of tumors, and that antibody fragments such as Fab', fab, $F(ab')_2$ and $F(ab)_2$ have faster targeting kinetics than intact immunoglobulin and much lower occurance of human immune responses compared to intact IgG molecules (especially column 1 at lines 14-20). US 5,670,132 discloses methods for using the disulfide bonds in the hinge region of antibody fragments as points to couple label to the antibody fragments after reducing the disulfide bonds. US 5,670,132 discloses that the reduced antibody fragments retain their immunospecificity and ability

to bind antigen. US 5,670,132 discloses that if it is desired that imaging be done with bivalent $F(ab')_2$ and $F(ab)_2$ fragments, it will be necessary to either partially reduce interchain disulfide bonds without further cleaving the fragment, or to thiolate the fragment by introduction of ligands containing thiol groups by conventional procedures (especially column 4 at lines 47-67 and column 5 at lines 1-15).

Peters teaches the presence of a free cysteine in albumin (especially paragraph spanning pages 164 and 165).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted albumin taught by US 5,714,142 and WO 98/00717 A2 for PEG in the antibody fragment conjugate of Delgado et al and to have linked to the antibody fragment, including one such as F(ab')2 or fab' taught by Delgado et al and by US 5,670,132 or the fab disclosed by US 5,670,132, to albumin using a linker such as such as optionally substituted hexylene disclosed by US 5,714,142 or the 6 carbon alkylene linker taught by WO 98/00717 A2, said linker being linked via the thiol at the free cysteine in albumin taught by Peters and the thiols created as per the disclosure of US 5,670,132 in the antibody fragments disclosed by US 5,670,132, and to have optionally covalently linked the conjugate to a label such as the label disclosed by US 5,670,132, i.e., a reporter group of instant claim 19.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the efficacy of drug delivery or tumor imaging agent such as taught by Delgado et al that is an antibody fragment such as taught by Delgado et al and US 5,670,132 by increasing the antigen binding capacity and half-life in circulation of the antibody fragment by coupling it to albumin via a linker such as optionally substituted hexylene disclosed by US 5,714,142 or the 6 carbon alkylene linker taught by WO 98/00717 A2 because Delgado et al teach that it desirable to increase plasma half-life of antibody fragments by reducing their renal clearance and therefore increasing plasma and tissue levels, US 5,714,142 discloses that albumin coupling is an effective approach to increasing half-life of small molecule drugs, peptides or proteins in pharmaceutical compositions because albumin is a large stable protein that is too large to be filtered through the kidneys, WO 98/00717 A2 teaches that conjugation of drugs to albumin via a 6 carbon alkylene linker molecule, said conjugation including at a thiol group bridged by a linking molecule results in increased half-life and greater specificity, Peters teaches the presence of a free cysteine in albumin, i.e., a thiol group, and US 5,670,132 teaches that the reduced cysteine residues, i.e., the thiol groups on the cysteine residues, in the hinge region of antibody fragments may be used to label the antibody fragments because those residues are not crucial to the ability of the fragments to retain their immunospecificity and ability to bind antigen, and hence by extension, those thiols are available for coupling to albumin because they are not critical for function. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have coupled albumin through the single free cysteine at position 34 taught by Peters

because that cysteine was available without requiring manipulation to reduce a pared disulfide bond and the conformation of albumin would remain unchanged, and further because US 5,714,142 discloses coupling albumin to a drug or peptide or protein, not multiple copies of drugs or proteins, Delgado et al teach conjugates containing just one antibody fragment, and WO 98/00171 A2 teaches when coupling is accomplished using hydroxyl groups, multiple copies of drug are incorporated per albumin molecule and/or up to half of the albumin molecules are not coupled with drug, i.e., position 34 of albumin presented a single attachment site that was easy to couple, and WO 98/00171 A2 teaches that coupling can be accomplished through thiol groups. With regard to the claim limitation recited in instant claims 14 and 21, "wherein the antibody fragment and albumin are indirectly linked by a bridging molecule of from around 10A to around 20A in length between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34", the instant specification discloses on page 27 at lines 9-13 that serum albumin has one cysteinyl residue that is not engaged in a disulphide bond, that being at position 34 in mature human albumin, and the optionally substituted hexylene disclosed by US 5,714,142 or the 6 carbon alkylene linker taught by WO 98/00717 A2 meet the length limitation recited in the said claims. Claim 17 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the fab at the CH_1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds, and because US 5,670,132 discloses introducing additional thiol groups to the bivalent $F(ab')_2$ and $F(ab)_2$ fragments.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
May 16, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600